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SKIN LESION AND DISEASES IN OBESITY - PART I: THE SKIN DISORDERS RELATED TO INSULIN RESISTANCE AND SECONDARY INFECTIONS

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ABSTRACT

Obesity is a growing problem in most developed countries and is responsible for a significant degree of morbidity and mortality. Based on the WHO recommendations, BMI between 25 and 29.99 indicates overweight; BMI above than or equal to 30 indicates obesity, and BMI above than or equal to 40 points shows severe or morbid obesity. Clinically, obesity is defined as the accumulation of excess body fat to the extent that it may have adverse effects on health.

The consequences of obesity is not only an increased risk of cardiovascular disease, diabetes, and cancer development, but also the occurrence of disorders affecting the skin and subcutaneous tissue. It causes a dysfunction of the epidermal-dermal barrier (secondary superinfection), increased secretion of sebum and sweat (↑ pH of sweat and the skin), abnormal micro- and macrocirculation, lymph circulation and delayed wound healing. These disturbations are the skin disorders related to insulin resistance (acanthosis nigricans, acrochordons, keratosis pilaris, hyperandrogenism, hirsutism), predisposition to mechanical injuries (plantar keratosis, stretch marks, cellulitis, lymphatic edema, chronic venous insufficiency) and secondary infections (intertrigo infections, yeast and fungal infections, bacterial inflammation of subcutaneous tissue). However obesity can exacerbate some diseases including psoriasis, acne inversa, gout, chronic venous insufficiency.

The purpose of this article is to highlight the association between obesity and dermatologic conditions. We presented skin diseases related to insulin resistance and secondary infections due to obesity.

Introduction

Obesity is a growing problem in most developed countries and is responsible for a significant degree of morbidity and mortality in the Western world. A simple indicator of obesity is BMI (Quetelet index). Based on the WHO recommendations, BMI between 25 and 29.99 indicates overweight; BMI above than or equal to 30 indicates obesity, and BMI above than or equal to 40 points shows severe or morbid obesity [Duarte et al., 2012; WHO, 2005]. Clinically, obesity is defined as the accumulation of excess body fat to the extent that it may have adverse effects on health. It is generally agreed that obesity exists when body fat percentage is greater than 25% in males and 30% in females [Romero-Corral et al., 2008; WHO, 2005].

Obesity has been recognized worldwide as a major health problem, for even a billion people [Tobin et al., 2013]. In the United States, overweight and obesity is found in up to 68% of population [Flegal et al., 2010]. In Poland, the study NATPOL III PLUS (2002) showed that 53% of adults are overweight or obese (aged over 45 years - 77%) and the mean BMI was 25.9 kg/m^2 [WHO, 2005].

Although genes predispose to develop obesity (mutations in the leptin gene and proopiomelanocortin), the environmental factors can influence it in 60 to 70%. These are: a high socioeconomic status, high-fat diets, sedentary lifestyles [Pi-Sunyer, 2002]. Chinese researchers discovered an interesting concept, concerning the role of human adenovirus 36 (HAdV-36) as the main pathogen of obesity. The studies showed that HAdV-36 may directly affect fat tissue with intensifying proliferation and differentiation of adipose stem cells in vivo/in vitro of animal models. Furthermore, HAdV-36 is engaged in the accumulation of triglycerides and reducing the production of leptin, increasing macrophage in fat tissue, reducing the secretion of corticosterone for an enhanced appetite and a further increase in body fat. However, the results about the relationship between obesity and HAdV-36 are still controversial in population studies [Xu et al., 2015].

The consequences of obesity is not only an increased risk of cardiovascular disease, diabetes, and cancer development, but also the occurrence of disorders affecting the skin and subcutaneous tissue. It causes a dysfunction of the epidermal-dermal barrier (secondary superinfection), increased secretion of sebum and sweat (↑ pH of sweat and the skin), abnormal micro- and macrocirculation, lymph circulation and delayed wound healing. These disturbations are the skin disorders related to insulin resistance (acanthosis nigricans, acrochordons, keratosis pilaris, hyperandrogenism, hirsutism), predisposition to mechanical injuries (plantar keratosis, stretch marks, cellulitis, lymphatic edema, chronic venous insufficiency) and secondary infections (intertrigo infections, yeast and fungal infections, bacterial inflammation of subcutaneous tissue). However obesity can exacerbate some diseases including psoriasis, acne inversa, gout, chronic venous insufficiency.

Obesity and physiology of the skin:

- dysfunction of the dermal-epidermal barrier (TEWL disorder);

Obesity affects the transepidermal water loss (TEWL). However, studies in obese people are not clear. In the study, Guido et al. found that the rate of TEWL on the forearm is lower in obese, especially with abdominal obesity, than in people with normal body weight, [Guida et al., 2010]. One of concept is that the leptin which is produced by fat tissue, is a mitogenic factor. It induces the proliferation of keratinocytes and fibroblasts with the intensification of the synthesis of collagen, thus strengthening the dermo-epidermal barrier [Guida et al., 2010; Li et al., 2005]. This may explain both the low rate of TEWL, the formation of fibroids and acanthosis nigricans. In contrast, Loffler et al., in adults and Nino et al. in children found a higher TEWL on the forearm according to the BMI as compared to the control group. [Loffler et al., 2002; Nino et al., 2012]. Perhaps obese children are more prone to overheating diaphoresis, because of the thick layer of subcutaneous fat [Nino et al., 2012].

- The sebaceous glands: ↑ free testosterone, IGF-1, insulin;

Androgens (testosterone and dihydrotestosterone) influence on sebum production through their receptors in the sebaceous glands, and dihydrotestosterone even 5-10-times stronger. This mechanism plays an important role in the pathogenesis of acne [Zoubolis, 2004]. Other factors contributing to increased activity of the sebaceous gland, are insulin and IGF-1. The concentrations of these hormones correlate with the overproduction of sebum, acne and activity levels of androgens [Cappel, et al., 2005; Kumari et al., 2013]. In addition, IGF-1 increases the sensitivity of the adrenal cortex to ACTH and induces the activity of key enzymes of the adrenal involved in the biosynthesis of dehydroepiandrosterone sulfate (DHEAS) [Cappel, et al., 2005; Kumari et al., 2013]. There is only one study evaluating the effect of a low calorie diet (1200 kcal) for the production of sebum in obese subjects. It is connected with a reduction of sebum secretion in 40%. Qualitative changes in lipid relate to a small amount of triglycerides, wax esters, cholesterol esters and cholesterol, and it doesn't change in the amount of squalene significantly [Pochi, et al., 1970]. Diet can also affect the function of the sebaceous gland with increase keratinocyte proliferation of the pilosebaceous follicle.

- Sweat glands: ↑ pH of sweat and skin;

Excessive sweating of obese due to the activity of the sweat glands apocrine and eccrine as well as the increased surface folds of the skin and a higher body temperature [Loffler et al., 2002; Yosipovich, et al., 2007]. Among them there are often bromhidrosis which occurs secondary to excessive secretion from either apocrine or eccrine glands. They become malodorous on bacterial breakdown because of bacteria that live in the folds (*Corynebacterium spp.*). They break secretions of the apocrine sweat glands to ammonia and short chain fatty acids, with a characteristic strong odour [Semkova, et al., 2015].

- Impaired lymphatic circulation, lymphedema;

Disturbances of micro- and macrocirculation (vasodilation and loss of response of the sympathetic nervous system)

- Delayed wound healing.

Skin diseases associated with obesity

The negative effects of obesity are associated not only with increased risk of diabetes, cardiovascular disease, obstructive sleep apnea, osteoarthritis, fatty liver disease and increased risk of cancer (especially colon, breast, uterus, prostate and pancreas) [Tobin et al., 2013]. The skin under the influence of weight gain becomes an arena for the development of specific diseases [Tobin et al., 2013]. The most common are: acanthosis nigricans (AN), acrochordons and plantar keratosis [Placencia-Gomez, et al., 2014]. Whereas, in the pediatric population acrochordons, stretch marks and plantar keratosis [Nino et al., 2012]. Brazilian research Boza et al., rated frequency of disorders of the skin and subcutaneous tissue in obese patients (BMI> 30) compared to patients with normal weight (BMI 18.5-24.9). They found that stretch marks, acanthosis nigricans and bacterial infections were correlated with BMI [Boza, et al., 2012]. Divyashree et al. confirmed the occurrence of the above disorders in individuals with a BMI > 30 [Divyashree, et al., 2014]. In contrast, 75% of patients with a BMI > 30 after the self complained is usually the occurrence of skin dryness and itching and problems with excessive sweating and skin irritation [Brown, et al., 2004].

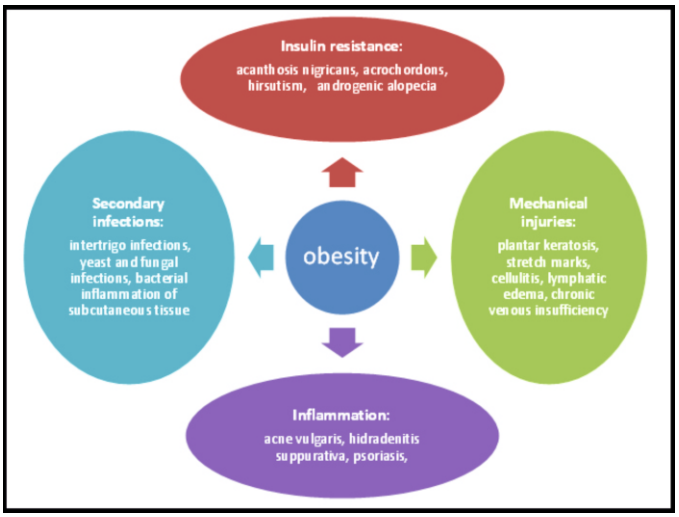

Fig. 1. Pathogenesis of skin diseases and disorders in obese people.

I. Skin diseases related to insulin resistance

Acanthosis nigricans (AN)

Acanthosis nigricans is an important cutaneous manifestation of insulin resistance, usually not related to cancer. [Schwartz and Janninger, 2011]. It typically has symmetric, hyperpigmented, hypertophic, verruccous and at times papillomatous patches or plaques that confer a velvety texture to the skin and are usually brownish-black in colour. The most commonly affected areas include the axillae, posterior neck fold, flexor surfaces of the upper and lower extremities, umbilicus, groin, inframammary folds, face, and perioral and perianal surfaces. In obese individuals, involvement of the maxillary and periorbital skin surfaces may be noticed, but this is more common in patients with generalized or malignancy-associated AN [Schwartz and Janninger, 2011]. The acrochordons often coexist in these lesions.

AN etiology is associated with activation of the receptors of EGF (Epidermal growth factor), IGF-1 (Insulin-like growth factor 1) and FGF (fibroblast growth factor), which belong to the family of tyrosine kinase receptors. Hyperinsulinemia due to insulin resistance activates these factors to induce proliferation of keratinocytes and fibroblasts [Barbato, et al., 2012; Napolitano, et al., 2015; Phiske, et., 2014; Schwartz and Janninger, 2011; Yosipovich, et al., 2007]. Hud et al., showed the presence of acanthosis nigricans with concomitant increase in plasma insulin levels in 74% of the obese. This disorder is more often found in women and dark-skinned blacks than in whites [Hud, et al. 1992]. In turn, the Wild study demonstrated a statistically significant association between the degree of obesity, acanthosis nigricans and diabetes [Wild, et al. 1995]. Similarly, in the pediatric population Ng et al. observed the presence of acanthosis nigricans in 54% of obese children [Ng, et al., 2014].

Acanthosis nigricans has been classified into eight types. They are benign (non-syndromic, insulin resistance-associated AN), obesity-related, syndromic, malignant (paraneoplastic), unilateral, acral, drug-induced, and mixed AN, a combination of two or more of the above. Only one of these types is a recognized as paraneoplastic syndrome [Phiske, et., 2014; Schwartz and Janninger, 2011].

Treatment of these lesions must be carried out with the combination of a low calorie diet and reduction of body weight. In addition, the formulations can be used to reduce the resistance to insulin with metformin or glitazones. Retinoids, calcipotriol and CO_2 laser are used in the topical treatment [Napolitano, et al., 2015; Yosipovich, et al., 2007].

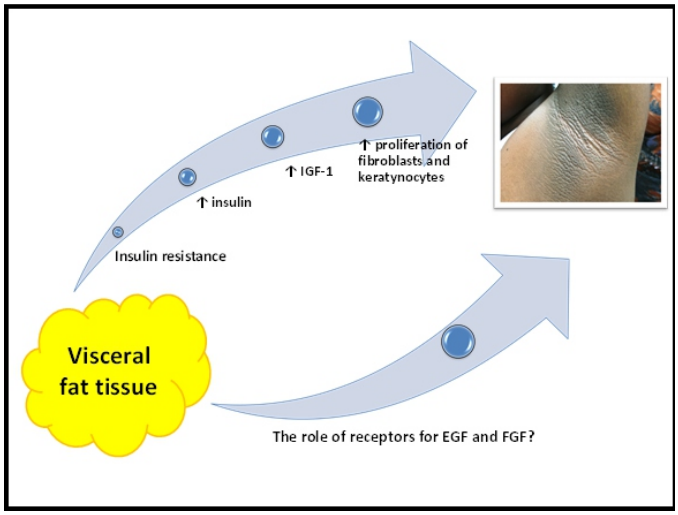

Fig. 2. The pathogenesis of acanthosis nigricans.

Fig. 3. Patient 32 years old, female, BMI 32.6 - acanthosis nigricans, fasting glucose 112 mg/dl.

Acrochordons (skin tags, fibromas)

Acrochordons occur in 20-25% of the population, and after 40 years of age, even in 37%. They are mainly located in the skin of the neck, eyelids, armpits and groin area. These are described in other rare locations: in the mucous membranes of the mouth, anus, vulva, penis. They have the color of the skin or in people with darker complexion from light to dark brown. Their size ranges from 1 millimeter to 1 centimeter. These are usually asymptomatic, and they do not become painful unless inflamed or irritated. Patients may complain of pruritus or discomfort when an acrochordon is snagged by jewellry or clothing. [El-Safoury, et al., 2013; Kishan Kumar, et al., 2013; Owczarczyk-Saczonek and Placek, 2016; Rajput, et al. 2013].

Three types of acrochordons are described, as follows:

- small, furrowed papules of approximately 1-2 mm, located mostly on the neck and the axillae;
- single or multiple filiform lesions of approximately 2 - 5 mm occurring elsewhere on the body;
- large, pedunculated tumor or nevoid, baglike, soft fibromas that occur on the lower part of the trunk [El-Safoury, et al., 2013; Kishan Kumar, et al., 2013; Rajput, et al. 2013; Schwartz, et al., 2004].

Acrochordons are benign tumors. On rare occasions, histological examination reveals a basal or squamous cell carcinoma [Schwartz, et al., 2004].

The presence of acrochordons is strongly associated with obesity, insulin resistance, atherogenic lipid profile, or metabolic syndrome. They can be a useful symptom indicating an increased risk of these diseases. Insulin activates IGF-1, which is acting on the receptors for EGF on the basal keratinocytes and fibroblasts, inducing them to proliferate [El-Safoury, et al., 2013; El-Safoury 2011, Idris, Shah]. Moreover, increased amount of EGF receptors in the acrochordons tissue is observe [Barbato, et al., 2012;, Jowkar, et al., 2010; El-Safoury, et al., 2013].

Hyperinsulinemia also increases ovarian androgens production, while IGF-1 and 2 reduce the production of SHBG (sex hormone-binding protein) in the liver, which contributes to the increase of free testosterone in the target cells. A higher expression of the receptors for androgens and estrogens (α and β) were found in the acrochordons tissue and on the keratinocytes too. Estradiol binds receptors on keratinocytes, which induce their proliferation and 17β-estradiol increase fibroblast proliferation [Bakry, et al., 2014; El-Safoury, et al. 2010; Owczarczyk-Saczonek and Placek, 2016].

Leptin responsible for the formation of acrochordons because it stimulates their receptors in the epidermis and dermis. This adipokin is produced primarily by adipocytes, and its concentration is directly proportional to body fat mass. Leptin increases insulin sensitivity and improves glucose tolerance but has also a mitogenic effect on keratinocytes [Owczarczyk-Saczonek and Placek, 2016; Stallmeyer, et al., 2001].

The formation of acrochordons is also caused by the presence of mast cells. It explain the location of acrochordons in regions susceptible to injuries. It was found that mast cells are recruited to sites of skin injury, where they release TNF-α, which can regulate keratinocyte apoptosis or stimulate their proliferation. Tryptase released from the mast cells is a potential fibroblast growth factor. Moreover, mast cells have estrogen receptors with high affinity [El-safoury, et al., 2011; da Silva, et al. 2014].

Finally, the concept formation of acrochordons is associated with the role of HPV. HPV types 6/11 DNA was detected in 88% of lesions [Dianzani et al., 1998]. It is believed that HPV following trauma, take part in their formation [Dianzanni et al., 1998; Gupta, et al., 2008].

Fig. 4. The patient 57 years old, female, BMI 31.55 - fibroid tumors on the eyelids and neck.

Hyperandrogenism in women

Obesity causes dysfunction of the endocrine system and leads to abnormalities of hormone levels in the blood. This is not only a disruption of secretion and metabolism, but also the transport of hormones and/or performance of their target tissues. The increase in mass of fat tissue primarily imbalance sex steroids in premenopausal women [Pasquali, et al., 2001]. The study of Azziz et al., which analyzed women with clinical hyperandrogenism (amenorrhea, ovulatory dysfunction, excessive hair growth, virilization, alopecia or acne), shoved that patient with androgens excess (serum testosterone, dehydroepiandrosterone sulfate, and 17-hydroxyprogesterone) were obese: 60% with BMI ≥ 30.0 kg/m^2 and 20% with morbid obesity BMI ≥ 40 kg/m^2 [Azziz, et al., 2004].

The main hormonal disturbances in obesity are:
functional hyperestrogenism in visceral obesity which leads to an increase in the release of LH (luteinizing hormone) by the pituitary gland, and increases ovarian androgen production then they are converted to estrogens in the fat tissue;

hyperinsulinemia as a consequence of obesity increases ovarian androgen production (increased 17α-hydroxylase in ovarian theca cells);

increased secretion of androgens and low concentrations of SHBG (sex hormone-binding globulin) cause a combination of functional ovarian hyperandrogenism, which cause of androgenetic alopecia and hirsutism in obese women [Krzyżanowska, 2012].

People with central obesity have a lower levels of SHBG. Testosterone is mainly related with albumin and SHBG, but insulin inhibits the synthesis of SHBG, thus there is increasing the amount of free testosterone in the serum [Krzyżanowska, 2012].

Insulin resistance leads to virilism. Hyperinsulinemia by affecting the hypothalamic-pituitary-adrenal gland, influence on increases production of adrenal androgens, and insulin directly affecting their receptors causes increased production of ovarian androgens [Olszanecka-Glinianowicz, et al., 2005]. Hyperandrogenism may also result from an increased production of endogenous androgens because of an increased adipose tissue mass. Moreover, there is synthesis of testosterone [Yosipovich, et al., 2007]. In addition, androgen receptors are regulated by the transcription factor FoxO1, insulin and IGF-1, which are also key factors associated with metabolic syndrome [Melnik, et al. 2013]. As a result of these hormonal disorders it is observed the development of facial hair, acne, acne inversa and androgenic alopecia. Ruutiainen et al. showed that hirsutism is correlated with BMI, regardless of age and level of testosterone [Ruutiainen, et al. 1988]. Treatment of hyperandrogenism is needs to control insulin levels, weight reduction, use of oral contraceptives and antiandrogenic [Yosipovich, et al., 2007].

In addition, increased production of lipids and hyperplasia of the sebaceous glands, and consequently increase the population of *Propionibacterium acnes* which are causes a severity of acne vulgaris and acne inversa [Picardo, et al., 2009; Zoubolis, 2004]. In addition testosterone increases the risk of stretch marks [Yosipovich, et al., 2007].

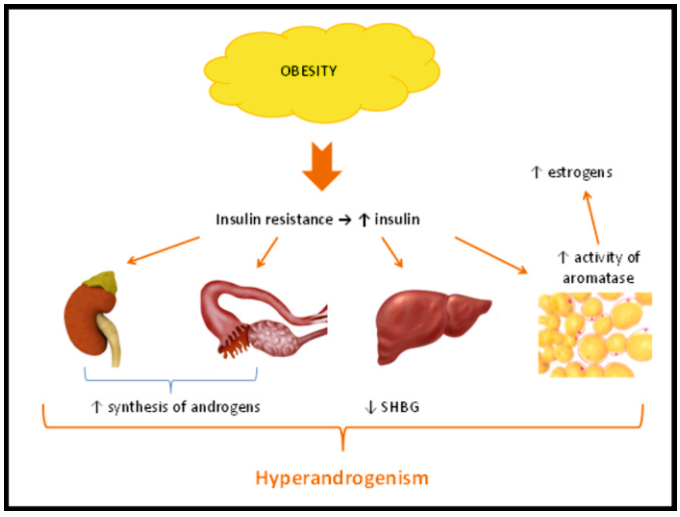

Fig. 5. Diagram of hyperandrogenism due to obesity.

Androgenic Alopecia (AGA)

The increase of BMI influences the severity of androgenetic alopecia (AGA), regardless of age and testosterone [Yang, et al., 2014]. There is a strong evidence that increased adipocytes affect the physiology of the pilosebaceous follicle, by the production of bone morphogenetic protein-2, leptin and adiponectin, which affects hair growth and hair cycle [Yang, et al., 2014; Minimari, et al. 2014].

Androgenetic alopecia is associated with an increased risk of coronary heart disease and a higher incidence of metabolic syndrome in men with early-onset. The study evaluating the incidence of AGA in young men under 35 years of age, showed a statistically significant association with obesity and waist circumference [Hirso, et al. 2007]. The study Gopinath et al. confirmed these disorders in men with AGA almost 3 times higher are compared to men without this disease [Gopinath and Upadya, 2016]. The mechanisms explaining the

relationship between early AGA and serious cardiovascular events, such as myocardial infarction or ischemic heart disease are not clear. Androgens receptors were found in vascular endothelium, but their role is unknown [Ozbas Gok, et al. 2015]. Lesko et al., examined 665 male patients with AGA and 772 control patients who had acute myocardial infarction under 55 years of age, showing the relationship of AGA and this disease [Lesko, et al., 1993]. In addition, the systolic blood pressure was significantly higher in the group with AGA. There are few studies proving the link between hypertension and serum aldosterone and AGA [Ozbas Gok, et al. 2015].

In women, the situation is similar. The study found a strong association of Korean women, who suffer from AGA with risk factors for cardiovascular diseases: BMI, waist circumference, hypertension, cigarette smoking, blood glucose, serum triglycerides and VDRL [Park, et al. 2016]. In contrast, a typical example of the prevalence of these disorders is polycystic ovary syndrome (PCOS), which co-exists with amenorrhoea, hirsutism, obesity, acne, androgenetic alopecia [Azziz, et al., 2006]. Iranian meta-analysis showed in overweight women with PCOS in 21%, and obesity in 19% the presence of hirsutism. The result of this syndrome is the development of insulin resistance in more than 1/3 of the patients and type 2 diabetes in 7,5% to 10% [Jalilian, et al., 2015]. In comparison American studies indicate the incidence of obesity in PCOS above in 60% of PCOS patients, and even in 73% of teens with BMI above the 95th percentile [Agapova et al., 2014]. In addition, it is believed that central android obesity is a risk factor PCOS [Jalilian, et al., 2015; Mor et al., 2004]. In turn, the British study reported that women with AGA and hirsutism as a result of PCOS have a higher levels of testosterone, androstenedione than control population [Ward, et al. 1978]. The weight loss in patients with PCOS results in significant and long-lasting improvement in the hormonal profile. A moderate reduction in body weight (approx. 10%) improves blood pressure, lipid profile and glucose, but to achieve improved hormonal profile weight reduction must be higher than 10% [Olszanecka-Glinianowicz, et al., 2005].

Therefore, early AGA can even be a component of metabolic syndrome (early detection of risk factors for cardiovascular diseases) [Bakry, et al. 2015].

II. Skin infections

Obesity increases the risk of skin infections for several reasons:

- excessive skin fold keep moisture which macerate and results in pathogenic bacteria development.
- lymphatic flow is impeded, reducing oxygenation of the surrounding tissue.
- skin pH is higher in obese, which increases the risk of *Candida* infections [Beitz, 2014].

Obesity is a common risk factor for secondary infections after surgery, and community-acquired infections, such as pneumonia, sepsis [Huttunen and Syrjänen, 2013]. Obesity can cause dysregulation of the immune system. In obese, number of macrophages in visceral fatty tissue, is higher than in the subcutaneous fatty tissue. Expanding adipocytes, due to hyperinsulinemia and insulin resistance, burst and die, releasing pro-inflammatory molecules including IL-6, oxygen free radicals (ROS) and free fatty acids. Thus activated macrophages in adipose tissue mobilize the transition of new vessels in the place of the dead fat cells. Macrophages release inflammatory MCP-1 and TNF-α, exacerbating inflammation in adipose tissue. They are the main source of TNF-α in adipose tissue inducible nitric oxide synthase and IL-6. A vicious circle mechanism is observe. Number of macrophage infiltration located around a dead adipocytes drasticly increases in obesity and can constitute up to 60% of the total cell number in adipose tissue [Davidovici, et al. 2010]. As a result is a reduction in the quantity of CD8 + and CD4 + NK cells, reducing the activity of dendritic cells, causes impaired of anti-infection immunity [Huttunen and Syrjänen, 2013].

Moreover, obesity causes disruption of the skin barrier, lymphatic system, the structure and function of collagen. Increased surface of the skin folds in obesity promotes infections, especially *Candida spp*. Lesions are localized mainly in the folds below the abdomen, groin, inframammary regions and intergluteal cleft. In these regions there is an increase perspiration and temperature which causes higher pH of sweat, increase friction (mechanical stimulation) and glucose concentration in the skin [Guida, et al., 2010; Yosipovich, et al., 2007]. The higher pH conducive to infection correlates with BMI in obese women. It is recommended to use cleaning agents with acid pH, topical antifungal therapy, and even oral medications in longe lasting infections (preferably fluconazole).

In addition intertrigo yeast develops erythrasma (*Corynebacterium minutissimum*), furunculosis (*Staphylococcus aureus*) and cellulitis (cellulitis). Obesity and concomitant lymphedema is a strong risk factor for erysipelas, cellulitis and necrotizing fasciitis. Among women hospitalized with necrotizing fasciitis even 88% were obese [Schipman, et al., 2011; Yosipovich, et al., 2007]. Additionally, hypertension and diabetes in obese cause the mortality rate as high as 50% [Francis, et al., 1993].

Athlete's foot and onychomycosis are also more common in obese patients, the triggering factors are vascular disorders and hyperglycemia. In addition, dermatophyte infections may complicate intertrigo [Yosipovich, et al., 2007].

Fig. 8. Patient 67 years old, female, 39,41 BMI, hypertension, hypertriglicydemia: the picture above - chronic candidiasis inframammary regions; picture below - stasis lymphedema, dryness and thickening of the skin and onychomycosis (*Trichophyton rubrum*).

Conclusions

The impact of obesity on the skin has received minimal attention. The purpose of this article is to highlight the association between obesity and dermatologic conditions. Skin lesions and disorders associated with obesity are symptoms of an increased risk of atherosclerosis and coronary artery disease too. Awareness of these disorders may help to diagnose the subclinical phase, and thus early implement the appropriate management for patients. The treatment of obesity is a difficult task and requires the action of multidisciplinary teams of physicians, dieticians, physiotherapists and psychologists. Knowledge of skin disorders and dermatological diseases in obese people is necessary because of global epidemic of obesity.

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